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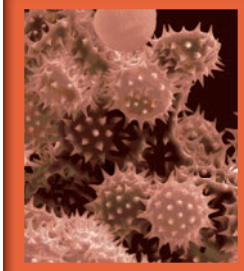

Pharmacologic Management of Allergic Conjunctivitis: An Evidence-Based Algorithm

Report of the Ad Hoc Committee for the Pharmacologic Management of Allergic Conjunctivitis

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RATIONALE FOR DEVELOPMENT

The ocular conjunctiva is among the mucosal surfaces most accessible to airborne allergens and is a very common site of allergic inflammation.[1] Millions of Americans—at least 30% of the population—are affected by allergies, often at a significant detriment to their quality of life and productivity at school and work.[1] While the importance of allergic conjunctivitis is often linked more to its frequency than its severity, symptoms of ocular pruritus, redness, and tearing can cause significant distress in moderate to severe cases.[2] Multiple surveys have shown that in patients with seasonal allergic conjunctivitis, ocular symptoms are at least as bothersome as nasal symptoms in a majority of patients who experience both.[3,4]

Despite its high prevalence and potential to diminish patient wellbeing, ocular allergy may be overlooked or undertreated by patients and healthcare practitioners.[4] When patients present with an array of allergy-related manifestations, practitioners may fail to appreciate the extent of ocular involvement. Patients who self-diagnose commonly fail to seek medical attention, even when relief from over-the-counter (OTC) remedies is inadequate.[4] Those who do seek medical care may incur significant out-of-pocket and insurance costs, and some remain unsatisfied with their care.[3]

The field of ocular allergy continues to advance. Family practice specialists, eyecare specialists, and allergists are equipped with topical medications—including dual-acting antihistamine/mast-cell stabilizers and ester-based corticosteroids.[5] Relief from allergic conjunctivitis symptoms—whether mild or severe—has become a feasible goal for nearly all patients.

This algorithm provides a clinical update on the subject of ocular allergic conditions and outlines current best practices regarding diagnosis and treatment of allergic conjunctivitis. It establishes a step-by-step, state-of-the-science approach to caring for patients with allergic conjunctivitis based on recent medical findings and expert opinion. Greater awareness of the allergic conjunctivitis disease state and knowledge of treatment options for symptom relief will improve patient management and move healthcare providers and patients closer to their goal of ameliorating symptoms of ocular allergy.

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GOALS OF THIS MANUSCRIPT

- To offer an overview of the epidemiology of ocular allergy in the US
- To review available categories of pharmacologic agents for the treatment of allergic conjunctivitis
- To distinguish among different allergic conjunctivitis conditions
- To outline current best practices regarding diagnosis and treatment of allergic conjunctivitis
- To suggest criteria for referral to a colleague with different expertise
- To provide a bibliography of literature supporting treatment recommendations

PROCESS OF ALGORITHM DEVELOPMENT

Management of Allergic Conjunctivitis: An Evidence-Based Algorithm is the result of collaboration among experts in optometry and in allergy/immunology. The content was developed from material in the PubMed database of English-language literature relevant to the topic and the clinical expertise of the committee.

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INTRODUCTION

Allergies are widespread in the US, affecting 30% or more of the population.[1] According to an analysis from 1993 to 2008, prescribing for allergic conditions has accelerated by approximately 20%.[2] This likely reflects an increasing prevalence of allergic disease in developed countries While the exact reason for this is not known, multiple factors are thought to play a role, including industrialization, urbanization, air pollution, climate change, and the "hygiene hypothesis" which attributes immune hypersensitivity among city-dwellers to low microbial exposure during childhood.[1,3,4] In addition, the epidemic of dry eye syndrome may be contributing to a rising incidence of conjunctival allergies, since a robust tear film is necessary to wash away allergens and irritants from the ocular surface.[5]

Presentation

Because ocular allergy may be described as one feature of a complex clinical presentation or, less commonly, as a distinct clinical entity in its own right, prevalence reports vary.[6] Typically, ocular allergy presents in conjunction with other systemic atopic manifestations, including rhinoconjunctivitis (or hayfever), rhinosinusitis, asthma, urticaria, or eczema.[1] Allergic rhinitis—considered by many the most common allergic disorder—is complicated by ocular symptoms in 50% to 75% of patients, according to multiple studies; and this may be increasing.[1,6,7] On the other hand, patients with systemic allergic inflammation may experience ocular symptoms as an isolated or predominant complaint; in the US this phenomenon is particularly common during summer months.[6] Among patients with a predominance of ocular symptoms, the term allergic conjunctivorhinitis may be more descriptive.[1]

Allergic conjunctivitis and rhinitis can exact a significant toll on patients. The most prominent symptom of allergic conjunctivitis is itching, which can range from mildly uncomfortable to severely bothersome. Itching and other common symptoms (which may include watery eyes, redness, pain and soreness, stinging, and swelling) may be detrimental to patients and reduce their ability to perform daily routines or activities at school or work.[6]

Seasonal vs Perennial Allergy

The two most common forms of ocular allergy are seasonal and perennial allergic conjunctivitis, and, of the two, seasonal is the more common.[8] Seasonal and perennial allergies differ according to the nature of the symptom-triggering allergens. Seasonal allergies are triggered by aeroallergens that have a seasonal periodicity, such as tree, grass, and weed pollens that abound in spring and fall.[1] Patients sensitive to those allergens tend to present most frequently during those seasons. Perennial allergies, by contrast, are triggered by environmental allergens commonly found in the home—such as

Committee members were allergists Leonard Bielory, MD, and Eli O. Meltzer, MD; and optometrists Jimmy D. Bartlett, OD, DSc, Ron Melton, OD, Kelly K. Nichols, OD, MPH, PhD, and Randall K. Thomas, OD, MPH. Establishing the committee and developing this treatment algorithm was sponsored Bausch + Lomb.

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dust mites, mold spores, or animal dander—and do not follow a seasonal distribution.[1] As a result, perennial allergies are problematic for patients all year long.

To a limited extent, distinguishing between seasonal and perennial allergies is useful. Perennial allergies may be more likely than seasonal to cause chronic inflammation due to the prolonged nature of the exposure. Patients may require allergy testing to determine which category and specific type of allergen is causing their distress, if history alone is insufficient for diagnosing specific allergens.[9] Identifying specific allergen sensitivities allows patients to minimize allergen exposure and enables immunotherapy when warranted.

However, despite a general congruence between types of allergens and the timing of the disease they cause, divergence from these patterns occurs commonly in real life, rendering the distinction between "seasonal" and "perennial" allergies somewhat academic. Patients with "seasonal" allergies may have symptoms for the majority of the year if they are sensitive to a perennial allergen, such as certain pollens; this is not uncommon in places like southern California, where many plants impart allergens to the air year-round. On the other hand, patients with allergies to cats or dogs—classically considered "perennial" triggers—may experience only intermittent exposures and present more like a "seasonal" allergy patient.

In both conditions, the body's pathophysiologic response to the allergen depends upon the phase of exposure rather than the nature of the triggering allergen. Thus, treatment is best devised according to the duration and severity of signs and symptoms regardless of whether the exposure is classically "seasonal" or "perennial."

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IMMUNE BASIS OF ALLERGIC CONJUNCTIVITIS

Patients with allergies experience exaggerated immune responses to allergens. Ocular allergies are characterized by type I (IgE mast-cell-mediated) and type IV (cell-mediated) hypersensitivity.[1]

In type I hypersensitivity, allergens activate B cells, which promote the release of IgE that subsequently sensitizes mast cells and basophils.[1] On re-exposure to the allergen, activated mast cells cause inflammation by: 1) releasing a host of preformed mediators, including histamine, from granules; and 2) generating newly formed mediators, including prostaglandins and leukotrienes, from membrane phospholipids.[1]

The full inflammatory cascade includes release of other immune mediators, including serotonin; eosinophil and neutrophil chemotactic factors; interleukins 4, 5, 6, 8, and 13; platelet activating factor; and tumor necrosis factor. Pathophysiologic consequences include increased vascular permeability, smooth muscle contraction, mucus secretion, and pruritus. Type I reactions occur in patients who have already been sensitized to an antigen, so the immediate phase commences within minutes of encountering the antigen. The late phase—which involves recruitment of tissue-damaging cells—may last for several days.[1]

Histamine is the main mediator of type I allergic reactions. In ocular tissue, histamine release induces itching, tearing, chemosis, edema of the conjunctiva and eyelids, blood vessel dilation, and papillary reaction (Figure 1).[1]

Type IV hypersensitivity is a cell-mediated process involving T-cells, cytokines, and macrophage activation. The response peaks at 48 to 72 hours (called "delayed" hypersensitivity) and results in tissue damage.[1]

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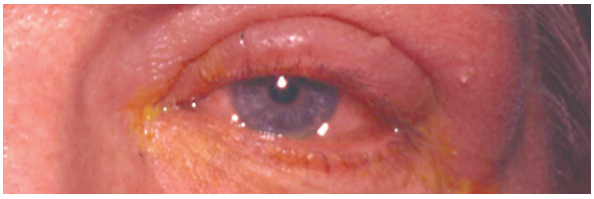
DIAGNOSIS

Signs and Symptoms

Symptoms of allergic conjunctivitis may fluctuate throughout the year, with exacerbations most likely during times of highest allergen exposure and in weather that is warm, windy, and dry. Patients with allergic conjunctivitis present with one or more signs and symptoms including itching, burning, stinging, redness, swelling, and tearing. Redness and itching are the most common symptoms. The *sine qua non* of allergic conjunctivitis is itching, and a diagnosis of allergic conjunctivitis should be called into question if a patient does not complain of ocular itch.[1]

Figure 1



Eyelid edema, conjunctival chemosis and injection, and watery discharge characteristic of a type I ocular allergic reaction. *(Image courtesy of Randall K. Thomas, OD, MPH, and Ron Melton, OD.)*

Itching may be particularly aggravating in the nasal quadrant of the eye and may range from mild to severe. Itching is less common in other ocular conditions, although patients with blepharitis, dry eye, or other conditions may complain of itching as well.[1]

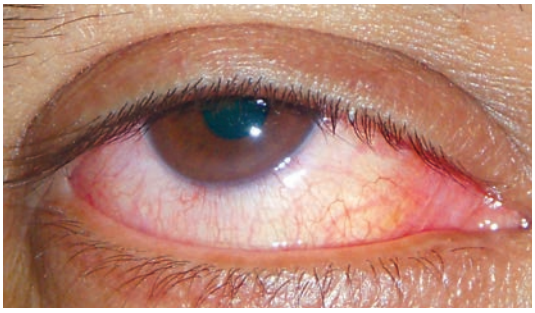
Discharge associated with allergic conjunctivitis is usually watery (and is frequently referred to simply as tearing) (Figure 2). The discharge may contain a small amount of mucus, making it stringy or ropey. Discharge associated with chronic allergy may be purulent or mucopurulent in nature and may trigger suspicion of bacterial conjunctivitis. As aeroallergens affect both eyes at once, bilateral involvement is far more common than unilateral; unilateral involvement, or a condition that begins unilaterally, is likely caused by infectious agents.

Since the nasal and ocular mucosal tissues react to allergens in a similar way, most patients with ocular complaints also have nasal symptoms. Among patients with seemingly isolated ocular symptoms, mild nasal or even lower respiratory symptoms can often be uncovered with further questioning.[1]

Medical History and Exposures

Additional aspects of the patient history may be useful in ruling out conditions that are unrelated to allergic conjunctivitis. Recent exposure to purulent conjunctivitis ("pink eye") or respiratory tract infections in home, school, or workplace may point toward an infectious cause. Topical ocular medications, including artificial tears or decongestants (or the preservatives in some ophthalmic preparations), may occasionally irritate or inflame the ocular surface tissues.[1,2]

Figure 2



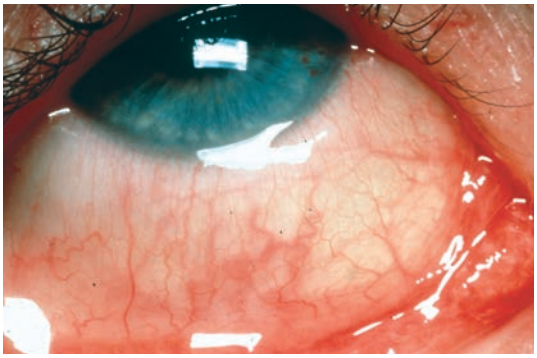
Allergic conjunctivitis with watery discharge. *(Image courtesy of Randall K. Thomas, OD, MPH, and Ron Melton, OD.)*

A history of allergic rhinitis, hayfever, asthma, or atopic dermatitis may commonly be noted in the patient and/or family members.[3] A medical history that is remarkable for systemic autoimmune disease (eg, rheumatoid arthritis) may suggest the associated condition: keratoconjunctivitis sicca.[1]

Physical Examination

Physical examination of patients suspected of having ocular allergy involves inspection of periocular and ocular tissues.[1] Eyelids should be examined for abnormalities, including evidence of blepharitis, dermatitis, meibomian gland dysfunction, swelling, discoloration, or spasm. Periorbital edema (eyelid swelling) that results from allergies may be more marked in the lower lid due to the effects of gravity. A dull blueish skin discoloration below the eye (an "allergic shiner") results from venous congestion and is present in some patients with allergies.[1]

Figure 3

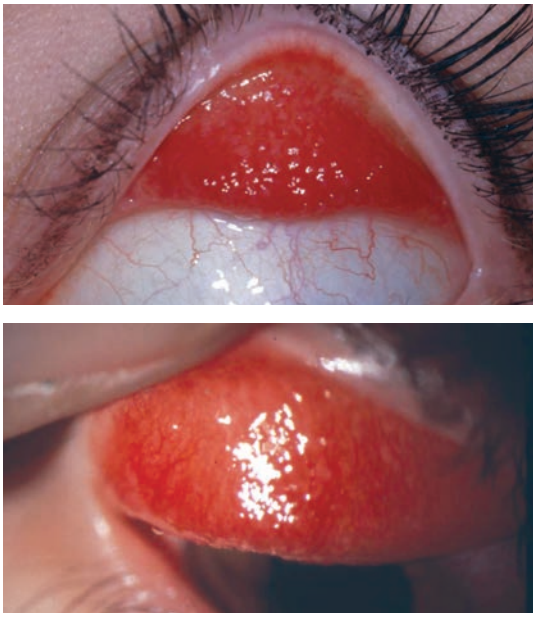


Conjunctival injection and chemosis in allergic conjunctivitis. *(Image courtesy of Jimmy Bartlett, OD, DSc.)*

The conjunctiva (palpebral and bulbar) should be inspected for abnormalities, such as chemosis, hyperemia, papillae, and the presence of secretions, although patients with allergic conjunctivitis frequently have unremarkable physical examinations.[1] Conjunctival injection (redness) may be mild to moderate. Swelling or chemosis may seem out of proportion to the amount of redness present and may be most noticeable at the plica semilunaris, the relatively loose area of bulbar conjunctiva at the nasal canthus (Figure 3). The palpebral conjunctiva in patients with allergic conjunctivitis tends to

have a milky or pale pink appearance, related to allergy-associated edema; by contrast, bacterial infections tend to produce a velvety, beef-red palpebral conjunctiva. Small, vascularized nodules (papillae) may be seen on the palpebral conjunctiva (Figure 4).[3]

Figure 4



Everting the lids may reveal papillae (small, vascularized nodules) in some patients with allergic conjunctivitis. *(Images courtesy of Randall K. Thomas, OD, MPH, and Ron Melton, OD.)*

Slit lamp examination by an eye-care professional can further facilitate the identification of conditions that may confound the diagnosis of acute allergic conjunctivitis.[1]

Differential Diagnosis and Comorbidities

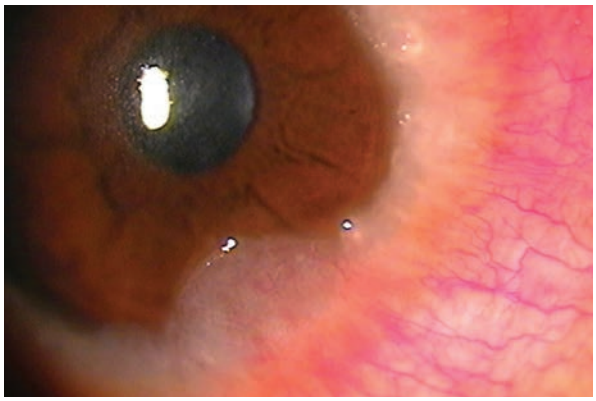
Seasonal and perennial allergic conjunctivitis must be distinguished from other more severe conditions — both allergic and nonallergic — with similar clinical characteristics. With careful history and examination, these conditions are unlikely to be misdiagnosed as acute allergic conjunctivitis.

Vernal keratoconjunctivitis and atopic keratoconjunctivitis are advanced forms of allergic conjunctivitis with unique characteristics and presentations. Vernal keratoconjunctivitis is named for its seasonal recurrence in spring and is characterized by chronic lymphocyte and mast-cell infiltration of the conjunctiva. Symptoms, including itching, are characteristically severe and can be triggered by dust, bright light, hot weather, and other nonspecific stimuli.[3] Inflammation of the palpebral conjunctiva can lead to the development of giant papillae on the tarsal conjunctiva, yellow-white points on the limbus (Horner's points) or conjunctiva (Trantas dots), lower eyelid creasing (Dennie's lines), pseudomembrane formation on the upper lid, and copious fibrinous discharge (Figures 5 and 6).[3]

Atopic keratoconjunctivitis, like vernal keratoconjunctivitis, is a chronic mast-cell-mediated allergic condition; a patient or family history of atopy (eg, eczema, asthma, or allergic rhinoconjunctivitis) is nearly always present and is central to making the diagnosis.[3] Symptoms of itching, tearing, and swelling in atopic patients tend to be much more severe than in patients with allergic conjunctivitis (Figure 7).[3]

As evident from their names, both vernal and atopic keratoconjunctivitis may involve the cornea and in severe, uncontrolled cases can cause significant visual impairment.[3]

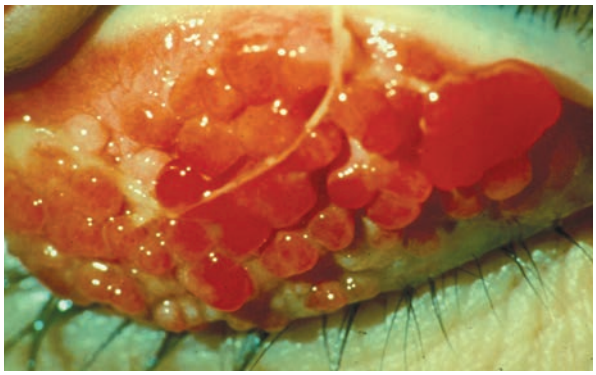
Figure 5



Trantas dots on the superior limbus are a manifestation of severe conjunctival allergy and inflammation. *(Image courtesy of Randall K. Thomas, OD, MPH, and Ron Melton, OD.)*

Other conditions to consider in the differential diagnosis of allergic conjunctivitis include giant papillary conjunctivitis (GPC), dry eye disease, anterior blepharitis, meibomian gland dysfunction (MGD), infectious conjunctivitis, conjunctivitis medicamentosa, and contact lens-related pathology. These conditions may also be comorbid in patients with allergic conjunctivitis.

Figure 6



Giant papillae and fibrinous discharge characteristic of vernal keratoconjunctivitis. *(Image courtesy of Jimmy Bartlett, OD, DSc.)*

Giant papillary conjunctivitis is a moderate to severe reaction to a contact lens or other stable ocular foreign body (eg, a suture or ocular prosthetic). Patients present with moderate to severe itching, blurred vision, inability to tolerate contact lens wear, conjunctival injection, and

white stringy discharge most noticeable in the morning. The condition derives its name from a characteristic finding on physical examination: large papillae ("cobblestoning") on the upper tarsal conjunctiva.[3]

Dry eye disease is the result of decreased aqueous tear production, increased tear evaporation, or abnormalities in tear composition.[4] Dry eye patients may complain of itching, burning, gritty feeling in the eye, sensitivity to light, ocular fatigue, and lowered tolerance for reading or night driving. Symptoms tend to progress throughout the day. The relationship between dry eye disease and allergic conjunctivitis is not entirely clear, and the two conditions often coexist. In these patients, dry eye may contribute to the pathogenesis, prevalence, and severity of the allergic conjunctivitis. A properly functioning tear film dilutes and removes many of environmental allergens that fall upon the ocular surface, reducing their chance of attaining a concentration sufficient to elicit an allergic response. However, as the tear film becomes more viscous or sticky, allergens become better able to collect on the ocular surface and can more easily reach the threshold for causing symptoms.[5]

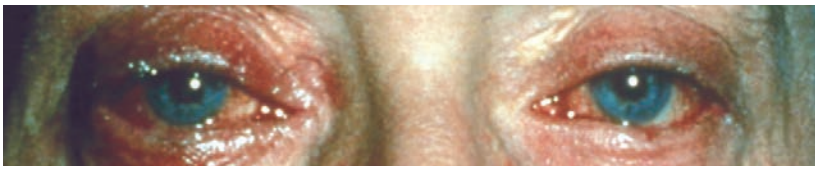
Itching is a classic presenting symptom in both allergic conjunctivitis and dry eye disease. A recent survey of optometry outpatients (N = 689) found that a majority of patients who had itchy eyes had clinically significant ocular dryness.[6] The same survey found a high degree of overlap in self-reported symptoms of itching, dryness, and redness among patients with allergic conjunctivitis, dry eye, or both.[6]

Since symptoms of dry eye and allergic conjunctivitis can be similar, it is important to assess whether a patient has isolated dry eye, isolated allergic conjunctivitis, or both. The diagnosis of dry eye is based primarily upon history and clinical examination, tear film osmolarity, tear film breakup time, or other tests.[7] Treatment depends upon the extent and severity of the disease and may include preventive measures or topical treatments such as lubricating tear substitutes, corticosteroids, or cyclosporine.[8]

Blepharoconjunctivitis Blepharitis describes inflammation of the eyelid due to infection or seborrhea, which can lead to secondary conjunctivitis ("blepharoconjunctivitis") in some instances. Patients complain of burning, itching, tearing, and a dry feeling in the eye. They may awaken with their eyes heavily crusted and notice debris and swelling of the lids.[9,10] When attributable to staphylococcal infection, examination reveals crusting around the base of the lashes; fine eyelid ulcerations at the base of the lashes may also be present.[9,10]

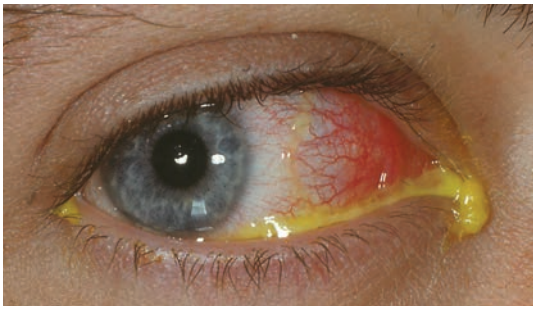
Infectious conjunctivitis Many infectious agents can cause conjunctivitis, including viral, bacterial, and fungal pathogens. Infectious conjunctivitis may be distinguished from allergic conjunctivitis by conducting a thorough history and physical examination. First, infectious conjunctivitis typically causes ocular burning, foreign body sensation, and stinging, rather than itching. Second, the pattern of ocular involvement is a distinguishing factor. Bacterial conjunctivitis is most commonly unilateral; viral conjunctivitis tends to start unilaterally and then spread to the other eye within a few days; while allergic conjunctivitis is nearly always bilateral. In addition, the quality and quantity of the discharge provides a diagnostic clue: In bacterial conjunctivitis, the discharge is thick and more purulent; in viral conjunctivitis, it is serous or watery; and in allergic conjunctivitis or dry eye, the discharge is typically scant and mucoid (Figure 8).

Figure 7



Severe redness and eyelid edema in a patient with atopic keratoconjunctivitis. *(Image courtesy of Jimmy Bartlett, OD, DSc.)*

Figure 8



Thick, purulent discharge helps differentiate bacterial conjunctivitis (pictured here) from allergic. *(Image courtesy of Jimmy Bartlett OD, DSc.)*

Patient Referral

Most patients with acute allergic conjunctivitis are returning patients with known disease and do not present diagnostic challenges. Some patients, however, may have comorbidities, symptoms that overlap with other conditions, or a constellation of signs and symptoms that are either more severe than the average allergic conjunctivitis patient or otherwise warrant a team approach to care.

Patients who have ocular involvement warranting examination by slit lamp biomicroscopy—such as those with photophobia, a corneal abnormality, or those on long-term corticosteroids—should be referred to an optometrist or ophthalmologist for a comprehensive workup and care plan. Patients suspected of having dry eye or an advanced allergic ocular condition, such as vernal or atopic keratoconjunctivitis or

GPC, likewise require referral to an eyecare specialist. Similarly, patients who have been treated with long-term oral steroids and are therefore at increased risk of intraocular pressure increases and cataract formation should also be seen by an eyecare specialist.

Patients who suffer from multisystem disease, including rhinitis or asthma, may benefit from referral to a specialist in allergy and immunology; and patients with allergies whose ocular manifestations are not well controlled may also benefit from referral. Allergen identification by skin prick or in vitro testing allows for more effective avoidance of allergens. To date, immunotherapy for desensitization to offending allergens is the only disease-modifying treatment available.

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TREATMENT: AVAILABLE AGENTS

Goals of Treatment The principal goal of treatment in allergic conjunctivitis is to reduce and control signs and symptoms. For most patients this means reducing itching; for others, reducing redness, swelling of the conjunctiva and/or eyelids, or other associated symptoms are also goals.

For patients with prolonged exposures to allergens and/or long duration of symptoms, an additional goal of treatment is to interrupt the cycle of inflammation and prevent further triggering of the inflammatory cascade.

Nonpharmaceutical Measures

Where possible, *allergen avoidance* is an obvious strategy. For many patients, however, avoiding the allergens that trigger their ocular symptoms may be difficult due to the unavoidable presence of the allergen source (eg, a family dog) or the number of allergens to which the patient is sensitive. However, when practical, minimizing allergen exposure is a reasonable and useful strategy for preventing symptoms.

Patients may be advised to use HEPA filters to remove airborne allergens from the home or office. Dust mite or animal dander control measures may be recommended. Patients seeking to avoid environmental allergens are advised to keep their home and car windows closed and use air conditioning for cooling. Simple protective measures such as wearing sunglasses as a mechanical barrier to aeroallergens and washing the hair in the evening prior to going to bed can help reduce allergen exposure.[1]

Regional climate greatly impacts the types of allergens to which patients are exposed. Allergen maps assist clinicians in predicting the timing of various natural allergens in their region. Furthermore, many local newspapers report daily pollen and mold counts, which vary yearly depending upon temperature, humidity, rainfall, and other weather patterns. While relocating to a different geographic region to avoid allergens is impractical and rarely advisable, awareness of the distribution and density of common allergens can help both clinicians and patients manage disease.

Physical Therapies

Patients with minimal or intermittent symptoms of allergic conjunctivitis may respond to non-pharmaceutical measures only. Application of a cold compress (for 10 to 15 minutes once or twice daily) may relieve symptoms—especially itching—for a small group of patients.

Instillation of OTC lubricating drops ("artificial tears") can bolster ocular defenses by flushing out antigens and can relieve mild ocular allergy symptoms. Benefits of these measures include simplicity, minimal expense, and a general lack of side effects.

Topical Ocular Decongestants

Topical ocular decongestants are synthetic adrenergic agonists that cause constriction of ocular blood vessels to reduce redness. Ocular decongestants are generally not recommended for the treatment of allergic conjunctivitis: They are effective in the acute management of redness, but do not affect the conjunctival response

to antigen and therefore have little effect on itching.[2,3] Intensive use of ocular decongestants (eg, multiple times daily over the course of one or more weeks) causes down-regulation of conjunctival alpha-1 receptors, resulting in "rebound hyperemia" once the medication is stopped.[3]

Occasionally, use of ocular decongestants may be warranted for cosmetic purposes. For patients who are not suffering from itching and who desire quick relief from redness, a brief regimen of low-dose ocular decongestant use (eg, two to four times per day for 1 to 2 days) is a reasonable recommendation. Ocular decongestants are contraindicated for patients with angle-closure glaucoma, and caution is advised for patients with cardiovascular disease, hyperthyroidism, and diabetes.[3,4]

Oral Antihistamines

Histamine is central to the type I hypersensitivity response and is a key mediator of allergy-related symptoms. Antihistamines act as inverse receptor agonists and competitively block the physiologic effects of histamine molecules that have not yet bound to a receptor, thereby decreasing capillary dilation, permeability, pruritus, and mucosal congestion. Because oral antihistamines do not block clinical manifestations already underway, onset of action is delayed due to systemic absorption, and they are best used adjunctively.[3]

Used orally, antihistamines provide systemic relief from allergic symptoms including itching and increased secretions. However, they may bind histamine receptors in unaffected tissues, leading to side effects of sedation, dry mouth, dry eye, hypotension, and tachycardia.[3] This is of greatest concern with first-generation oral antihistamines. Second-generation agents have lower lipid solubility, which reduces their ability to penetrate the blood-brain barrier, improving their side-effect profile particularly with regard to sedation.[3]

A significant proportion of patients with ocular allergy complain of dryness related to their allergies or have comorbid dry eye symptoms. Oral antihistamines may exacerbate rather than relieve their symptoms; such patients may benefit from discontinuing therapy with oral antihistamines. Most oral antihistamines are available over the counter, although some second-generation agents require a prescription.[3]

H1 antagonists are contraindicated in nursing mothers and expectant mothers in the third trimester, and caution is advised through all stages of pregnancy.[3] Sedating antihistamines require appropriate avoidance of other sedating substances, including alcohol and opioid analgesics; and working with dangerous machinery while taking these agents should be avoided. Patients with peptic ulcer disease, prostate hypertrophy, genitourinary or intestinal obstruction, or risk for acute angle-closure glaucoma should exercise caution with first-generation antihistamines with strong anticholinergic properties (clemastine, diphenhydramine, and promethazine).[3]

Topical Ocular Antihistamines (Single-acting)

Topical ophthalmic agents for the treatment of ocular allergy have a more rapid onset of action compared with oral antihistamines and are generally better tolerated.[3,5] Topical antihistamines do not access systemic cholinergic receptors, so, unlike oral antihistamines, they do not cause significant systemic side effects and generally do not contribute to ocular dryness. Topical antihistamines (eg, antazoline and pheniramine) are available over the counter in combination with the decongestant naphazoline.

These agents are nonselective, targeting both H1 and H2 receptors. Agents developed later are selective for allergy-mediated pathways and therefore less likely to cause adverse effects compared with nonselective agents. An example is emedastine, which is selective for H1 receptors and is available by prescription.[3]

Compared with placebo, topical antihistamines have been shown to significantly reduce signs and symptoms of conjunctivitis induced by allergen challenge in clinical trials.[3] These agents possess a single mechanism of action (MOA) and therefore affect only one of the two pathways involved in type I hypersensitivity. Like all antihistamine agents, topical antihistamines are contraindicated in patients at risk for angle-closure glaucoma.[3]

Topical Ocular NSAIDs

Topical ophthalmic nonsteroidal antiinflamatory drugs (NSAIDs) were initially used in perioperative cataract care and found serendipitously to reduce symptoms associated with allergic conjunctivitis. Ketorolac is the only NSAID approved for the topical treatment of seasonal allergic conjunctivitis.[6]

NSAIDs interfere with the second pathway in type I hypersensitivity, that of prostaglandin production. In the experience of the committee, due to the availability of agents with established efficacy and proven comfort profiles, ophthal-

mic ketorolac is used sparingly in the treatment of acute allergic conjunctivitis.

Topical Mast-cell Stabilizers (Single-acting)

Ophthalmic mast-cell stabilizers work by stabilizing mast-cell membranes and preventing degranulation associated with type I hypersensitivity reactions. By preventing mast-cell degranulation, these agents may reduce the influx of various inflammatory cells, including eosinophils, neutrophils, and monocytes.[7] Mast-cell stabilizers have been shown to decrease itching, tearing, and overall disease in clinical trials in comparison to placebo.[8,9]

In the experience of the committee, single-acting mast-cell stabilizers are now rarely used in the treatment of acute allergic conjunctivitis because they are slow to act; it may take 3 to 5 days before symptoms abate.[7] Pemirolast and nedocromil carry an indication for itching due to seasonal allergic conjunctivitis; cromolyn sodium and lodoxamide are indicated for vernal keratoconjunctivitis. Nedocromil may be taken twice daily, whereas the other agents require more frequent administration.[3]

Topical Dual-acting Antihistamine/ Mast-cell Stabilizers

Dual-acting antihistamine/mast-cell stabilizers are the most recently developed class of agents for the treatment of allergy-associated ocular itching. In a single molecule, they combine the mechanisms of two established classes: antihistamines and mast-cell stabilizing agents. These dual-acting agents reduce allergic inflammation by preventing mast cell release of inflammatory mediators and by selectively blocking the H1 receptor, thus countering the effects of histamine that has already been released—and enabling rapid onset of action.[3]

Selectivity for the H1 receptor decreases rates of adverse events such as drowsiness and dryness associated with nontherapeutic binding to other receptors.[10] In addition, these agents stabilize and prevent the degranulation of mast cells, thus interrupting the inflammatory cascade near its root and reducing symptoms over the long term.[3]

In clinical trials, dual-acting agents have been shown to effectively reduce itching associated with allergic conjunctivitis with greater duration of effect and better tolerability than single-action antihistamines.[11] Agents approved for the treatment of itching in association with allergic conjunctivitis include: ketotifen, azelastine, epinastine, olopatadine 0.2%, bepotastine besilate 1.5% (BEPREVE®), and alcaftadine 0.25%. Olopatadine 0.1% is indicated for the treatment of signs and symptoms of allergic conjunctivitis.[12] With the exception of sensitivity to any of the drug components, there are no contraindications to the use of these topical antihistamine/mast-cell stabilizing agents.[3] Most patients with itching associated with acute allergic conjunctivitis will benefit from treatment with a dual-acting antihistamine/mast-cell stabilizing agent.

Topical Ophthalmic Steroids

As a class, steroids have multiple sites and mechanisms of action, affecting virtually every part of the inflammatory cascade. Steroids inhibit both early and late phase allergic response; they suppress mast cell proliferation, inhibit cell-mediated immune responses, and block the production of all of the inflammatory chemical mediators, including prostaglandins, leukotrienes, and platelet activating factor.[13] Their broad action allows for relief of many ocular symptoms and signs associated with seasonal allergic conjunctivitis. Patients with moderate to severe manifestations of seasonal allergic conjunctivitis, prolonged or repeated allergen exposures, and those with prolonged symptoms are likely to experience both early and late phase inflammatory processes. Treatment with an appropriate topical ophthalmic steroid may be warranted in these patients.

The side effect profile of topical ophthalmic steroids has historically meant that they were reserved for patients with advanced or recalcitrant forms of ocular allergy. However, that paradigm changed when a class of steroid was in-

troduced with a key modification in its chemical structure: an ester group at carbon-20 in place of a ketone group at that location. Ester-based steroids have unique pharmacokinetic properties that cause the unbound drug to be rapidly metabolized, lowering the risk of steroid-induced side effects, compared with steroids that have a ketone group at carbon-20.[13]

Loteprednol etabonate (available as a 0.2% ophthalmic suspension [ALREX®]) is an ophthalmic ester steroid. Furthermore, ALREX® is specifically approved by the FDA for the temporary relief of the signs and symptoms associated with seasonal allergic conjunctivitis. For its record of efficacy and safety, ALREX® is a good choice for the treatment of seasonal allergic conjunctivitis.[14,15]

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ALGORITHM FOR THE MANAGEMENT OF ALLERGIC CONJUNCTIVITIS

Clinical practice guidelines provide a framework for choosing appropriate courses of management for individual patients based on categorization of patient characteristics. Comprehensive clinical guidelines that have been developed for the management of allergic rhinitis and asthma categorize patients according to severity of illness and other factors.[1,2] Based upon that model, the following algorithm represents a synthesis of the clinical expertise of the committee members and a review of relevant aspects of the literature and offers a concise guideline for the management of seasonal allergic conjunctivitis.

Patient Assessment

Appropriate management of allergic conjunctivitis should result in prompt relief of

Algorithm for the management of seasonal allergic conjunctivitis				
	LEVEL 1	**LEVEL 2**	**LEVEL 3**	**Notes**
MAIN FACTORS				
Itching	Mild	Mild to Severe	Moderate to Severe	If severe, consider alternative diagnosis (eg, vernal, atopic, or GPC)
	Intermittent	Intermittent to Persistent	Persistent	
Redness	Absent	Absent	Moderate to Severe	If severe, consider alternative diagnosis (eg, infectious conjunctivitis)
SUPPORTIVE FACTORS				
Foreign body sensation, tearing, burning, and/or other symptoms	Absent	Absent	Moderate to Severe	For dryness, inquire about oral antihistamines (may contribute to ocular dryness); consider diagnosis of comorbid DES
Symptom duration	Days	Days to Weeks	Weeks to Months	
Prior treatments	None	None or OTC medications not tolerated or not effective	Previous therapy tried	
TREATMENT				
First-line	Cold compress, artificial tears	AH/MCS (eg, BEPREVE® [bepotastine besilate ophthalmic solution] 1.5%*)	Topical steroid (eg, ALREX® [loteprednol etabonate ophthalmic suspension] 0.2%**)	
Alternatives	(a) Short-term topical OTC treatment, or (b) AH/MCS (eg, BEPREVE® ophthalmic solution*)			
FOLLOW-UP				
Clinic visit/IOP assessment	As needed	As needed	At 10 to 14 days Then every 2 to 4 weeks through week 6 Then every 3 to 6 months while using steroid	
Complete ophthalmic exam with dilation	Yearly or as needed	Yearly or as needed	Yearly	

GPC = giant papillary conjunctivitis; DES = dry eye syndrome; OTC = over-the-counter; AH/MCS = antihistamine/mast-cell stabilizer; IOP = intraocular pressure

* BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is administered as one drop in affected eye(s) twice daily. Contact lenses should be removed when administering BEPREVE® and may be replaced after at least 10 minutes to a non-red eye. Safety and efficacy of BEPREVE® has not been established in children under the age of 2 years.

** ALREX® (loteprednol etabonate ophthalmic suspension) 0.2% is administered as one drop in affected eye(s) four times per day. Contact lenses should be removed when administering ALREX® and may be replaced after at least 10 minutes to a non-red eye. Patients using ALREX® for greater than 10 days should have IOP monitored. Safety and effectiveness of ALREX® in pediatric patients have not been established.

Please see Important Risk Information for BEPREVE® and ALREX® on pages 10–11 and 14–15.

patients' symptoms.

Assessment begins with a careful patient history and clinical examination looking for severity of itching (mild, moderate, or severe) and whether the itch is intermittent or persistent. Severe itching should lead the clinician to consider the possibility of a serious ocular allergic condition, such as vernal or atopic keratoconjunctivitis.[3] In addition, other ocular symptoms, such as foreign body sensation, tearing, and burning, should be addressed. The presence and severity of conjunctival redness should also be assessed. Severe unilateral redness may indicate the presence of infectious conjunctivitis.

Patient characteristics may be sorted into one of three levels of involvement. In Level 1, itching is mild and either intermittent or of short duration. In Level 2, itching may be mild, moderate, or severe, and either intermittent or chronic. Redness is absent and symptom duration is moderate (from a few days to 2 weeks). In Level 3, itching may be moderate to severe and chronic and redness may be present.

In addition to these criteria, the presence of additional symptoms, including foreign body sensation, tearing, and burning may contribute to the overall severity of the presentation. Use of prior treatments should be considered. Patients with significant complaints of dryness that is worse at night (or related symptoms such as foreign body sensation) may have dry eye disease in addition to (or instead of) allergic conjunctivitis. Evaluation of the patient's dry eye may be warranted. Also, some OTC or prescription medications may contribute to symptoms of ocular dryness. Patients experiencing symptoms of dry mouth and dry eye due to oral antihistamines may benefit from cessation of that therapy.

Patients with ocular allergies should be asked about extraocular symptoms including nasal congestion, rhinorrhea, sneezing, coughing, wheezing, and skin rash. Signs or symptoms of systemic allergies should prompt referral to an allergist for a comprehensive allergy assessment.

Treatment

Level 1: Patients with mild, intermittent itching may use nonpharmaceutical measures such as cold compresses and lubricating ophthalmic drops. Alternatively, OTC medication or an antihistamine/mast-cell stabilizer may be prescribed. Based on the rationale outlined in this review, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% can be recommended.

Level 2: This group includes patients with itching (ranging from mild to severe and from intermittent to prolonged) who do not have redness. Treatment with BEPREVE® is appropriate, with other agents in this class as alternatives.

Level 3: For seasonal allergy patients with moderate to severe symptoms and redness, treatment with ALREX® (loteprednol etabonate ophthalmic suspension) 0.2% can be recommended. Patients whose symptoms are persistent can also be considered for treatment with ALREX®.

Prescribing of ALREX®

Treatment with an ester steroid is appropriate and may be prescribed with confidence for Level 3 patients. The chemical structure of loteprednol etabonate was designed so that the active drug is rapidly hydrolyzed to nonreactive metabolites. Following the basic tenets of steroid prescribing will help ensure safety for patients treated with ALREX®.

Patients placed on a topical ocular steroid should receive careful follow-up to assess efficacy and rule out adverse effects, such as drug-induced IOP elevation. IOP should be assessed prior to initiation of treatment. If steroid therapy continues beyond 10 days, IOP should be monitored beginning at day 14. A slit lamp examination of the ocular surface can rule out opportunistic infections (eg, with herpes simplex virus or fungi).[4]

A visit 2 to 4 weeks after the initial follow-up is recommended. Most steroid responders will have shown evidence of increased IOP by 4 to 6 weeks following initiation of therapy, so once that window has passed, it is safe to follow patients at longer intervals.[4] While taking any corticosteroid, patients should be followed at 3- to 6-month intervals. It is important to refrain from allowing refills during that time so that compliance with the follow-up schedule is enforced and adverse effects can be detected.

Studies have not found even long-term therapy with loteprednol etabonate 0.2% to be associated with the development of cataracts.[4] However, it is good practice for every patient to annually undergo a complete ophthalmic examination with dilation to look for signs of posterior subcapsular cataract development and other conditions.

It is always best to use the shortest course of therapy that effectively suppresses signs and

Prescribing of a topical corticosteroid for the treatment of seasonal allergic conjunctivitis:

1. Choose a steroid approved for the treatment of seasonal allergic conjunctivitis
2. Monitor IOP, especially within the initial 2 to 8 weeks of treatment
3. Refill prescriptions only at follow-up visits
4. Use the shortest effective course of therapy

Please see the full prescribing information for BEPREVE® and ALREX® on pages 17 and 19.

symptoms. In addition, stepping down to a Level 2 treatment should be considered when a patient's symptoms and signs are well controlled.

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BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% in the Treatment of Allergic Conjunctivitis

BEPREVE® merits consideration when choosing a treatment for mild to severe itching related to allergic conjunctivitis. BEPREVE® was approved by the FDA for the treatment of itching associated with allergic conjunctivitis in 2009, giving clinicians an additional option for their patients seeking fast, effective relief. Development of the ophthalmic formulation (BEPREVE®) stemmed from the success of oral bepotastine, which has been used to treat allergic rhinitis and related conditions in Japan since 2000.[1]

BEPREVE® targets multiple sites in early and late phases of the inflammatory cascade.[2] Like all members of its class, BEPREVE® blocks histamine receptors and stabilizes mast cells to prevent the further release of histamine and other mediators. In addition, BEPREVE® inhibits the generation of leukotrienes, platelet-activating factor, and interleukin-5 and suppresses recruitment of eosinophils into inflamed tissue.[1,2] Risk for side effects is minimized by the high selectivity for the H1 receptor and minimal extraneous binding to H3, adrenergic, muscarinic, benzodiazepine, and serotonin receptors.[2]

BEPREVE® has been shown to reduce allergy-mediated ocular itching rapidly and with long effect. In multiple clinical trials, patients treated with bepotastine 1.5% experienced significant reduction in ocular itching within 3 minutes of conjunctival allergen challenge (CAC).[1,3,4] In two studies, a rapid response was observed whether the exposure occurred 15 minutes or 8 hours after the medication was instilled, indicating a long duration of effect.[1,3]

Patients with mild, moderate, or severe itching respond favorably to BEPREVE®. In clinical trials, treatment with BEPREVE® resulted in a rapid and sustained reduction of symptoms, even when patients with severe symptoms were analyzed separately.[4,5]

Differentiating BEPREVE®

Pharmacokinetic properties and dosing schedules determine duration of effect and help to distinguish different agents within the dual-acting antihistamine/mast-cell stabilizer class. Once-daily dosing is available with alcaftadine and olopatadine 0.2%; other agents in the class, including BEPREVE®, are dosed twice daily.[6]

BEPREVE® is formulated in a lubricating base, making it comfortable on instillation. In clinical trials, patients report placebo-like levels of comfort on instillation.[3]

Product cost is an important factor to many patients. Generic ketotifen is the least expensive agent in this class; for some patients BEPREVE® is the least expensive on-patent antihistamine/mast-cell stabilizer.[7] BEPREVE® is available in a 10-mL bottle—the largest volume dispensed among the agents in this class—which allows a larger quantity to be purchased for a single copay. A single bottle may provide patients with enough medication for a whole "season" of allergies.[7]

Why BEPREVE®?

Among the agents available, BEPREVE offers the following features and benefits:

- History of safe and effective use of bepotastine molecule as systemic antiallergy agent prior to its development as topical ophthalmic agent[1]
- Highly selective for H1 receptor[2]
- Established efficacy in clinical trials, even among patients with severe itching[3,4]
- Established safety and tolerability[2]
- Rapid onset of action[1]
- Long duration of effect[1]
- Comfortable on the eye[3]
- Large bottle size

Important Risk Information

- BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients. BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to any surface. Keep the bottle closed when not in use. BEPREVE® should not be used to treat contact lens-related irritation. Remove contact lenses prior to instillation of BEPREVE®.
- The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%–5% of patients were eye irritation, headache, and nasopharyngitis.

Note: BEPREVE® has not been tested in children below the age of 2 years or in pregnant women.

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Please see the full prescribing information for BEPREVE® and ALREX® on pages 17 and 19.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Contraindications (4) 06/2012

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop into the affected eye(s) twice a day (BID). (2)

----------DOSAGE FORMS AND STRENGTHS--------
Solution containing bepotastine besilate, 1.5%. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated. at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

4 CONTRAINDICATIONS
Bepreve is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red. BEPREVE should not be used to treat contact lens-related irritation.

BEPREVE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

5.3 Topical Ophthalmic Use Only
BEPREVE is for topical ophthalmic use only.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

There are no adequate and well-controlled studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

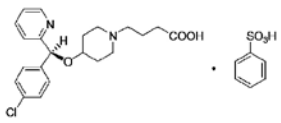
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use
Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

8.5 Geriatric Use
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11 DESCRIPTION
BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE contains 15 mg bepotastine besilate.
Bepotastine besilate is designated chemically as (+) -4-[[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.
The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.
Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics
Absorption: The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four times daily (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentration at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.

Distribution: The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use. The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

14 CLINICAL STUDIES
Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 hours post dosing of BEPREVE.

The safety of BEPREVE was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following size:
5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

STORAGE
Store at 15° – 25°C (59° – 77°F).

17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

Manufactured by: Bausch & Lomb Incorporated
Tampa, FL 33637
Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

Bausch & Lomb

Alrex®

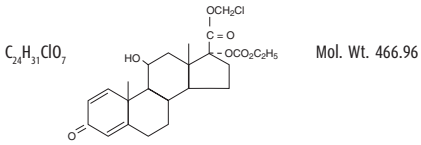
loteprednol etabonate
ophthalmic suspension 0.2%

STERILE OPHTHALMIC SUSPENSION

Rx only

DESCRIPTION:
ALREX® (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical Name:
chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains:
ACTIVE: Loteprednol Etabonate 2 mg (0.2%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.4-5.5. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with ALREX.

Clinical Studies:
In two double-masked, placebo-controlled six-week environmental studies of 268 patients with seasonal allergic conjunctivitis, ALREX, when dosed four times per day was superior to placebo in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. ALREX provided reduction in bulbar conjunctival injection and itching, beginning approximately 2 hours after instillation of the first dose and throughout the first 14 days of treatment.

INDICATIONS AND USAGE:
ALREX Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS:
ALREX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. ALREX is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS:
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

PRECAUTIONS:
General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. ALREX should not be used to treat contact lens related irritation. The preservative in ALREX, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red**, should be instructed to wait at least ten minutes after instilling ALREX before they insert their contact lenses.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. ALREX Ophthalmic Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALREX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

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Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% - 0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with ALREX, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with ALREX and 1% (1/135) with placebo.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.
One drop instilled into the affected eye(s) four times daily.

HOW SUPPLIED:
ALREX® (loteprednol etabonate ophthalmic suspension, 0.2%) is supplied in a plastic bottle with a controlled drop tip in the following sizes:
5 mL (NDC 24208-353-05) - AB35307
10 mL (NDC 24208-353-10) - AB35309

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" AND YELLOW IS NOT INTACT.

Storage: Store upright between 15°–25°C (59°–77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Revised August 2008.

Bausch & Lomb Incorporated, Tampa, Florida 33637
U.S. Patent No. 4,996,335
U.S. Patent No. 5,540,930
U.S. Patent No. 5,747,061

Based on full prescribing information revised August 2008.

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